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EXAMINER	
BAUSCH, SARAH L	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/663,497	MCINTIRE ET AL.	
	Examiner	Art Unit	
	SARAE BAUSCH	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,8 and 20-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8 and 20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1-4, 7-8 and 20-23 are pending in the instant application. Claims 5-6 and 9-19 have been canceled. Claims 2-3 are withdrawn. All the amendments and arguments have been thoroughly reviewed but were found insufficient to place the instantly examined claims in condition for allowance. The following rejections are either newly presented, as necessitated by amendment, or are reiterated from the previous office action. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is Final

Withdrawn Rejection

2. The rejections of claim 23, under 35 U.S.C. 112, 1st paragraph, new matter, made in section 5, of the previous office action mailed 03/05/2008 is withdrawn in view of the amendment to the claims.

Maintained Rejections

Claim Rejections - 35 USC § 112-Enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 4, 7-8 and 20-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method for determining a Caucasian or Asian's predisposition to atopy protection by detecting the presence of homozygous polymorphism of

157insMTTTVP (polymorphism 1, SEQ ID No. 22), of TIM-1 in a hepatitis virus A positive Caucasian individual, wherein the presence of the MTTTVP insertion is indicative of a Caucasian's predisposition to protect against atopy, does not reasonably provide enablement for a method for screening for a human individual's predisposition to any atopy by analyzing for the presence of any TIM-1 polymorphism. This rejection was previously presented in section 8 of the previous office action mailed 03/05/2008 and is reiterated below.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims

The claims are drawn to a method for the screening for a human individual's predisposition to atopy by analyzing the presence of at least one TIM-1 polymorphism wherein the presence of the polymorphism is indicative of an individual's predisposition to develop an atopy. The claims are further drawn to a method of contacting a biological sample with a probe

that specifically binds to the nucleic acid sequence of MTTTVP or a polymorphism in exon 3 of TIM-1 gene and further comprising the step of analyzing an individual for the presence of hepatitis A virus seropositivity.

The rejected claims encompass analysis of a human. The rejected claims encompass any type of atopy and detection of any polymorphism in TIM-1.

The nature of the claims requires knowledge of a correlation between detection of the presence of a TIM-1 polymorphism and predisposition to develop atopy.

Guidance in the Specification and Working Examples

The specification asserts that polymorphisms in the human TIM-1 gene and exposure to Hepatitis A Virus(HAV) are shown to be associated with protection from the development of immunological disorders, such as atopy. The specification asserts that a common polymorphism of TIM-1 in major human population has an insertion at position 157, 157insMTTTVP and HAV seropositivity protects against atopy but only in individuals with 157 insMTTTVP allele. The specification asserts that in some aspects the atopic disease is allergic rhinitis, atopic dermatitis, or asthma (see page 2, paragraph 6).

The specification asserts that polymorphisms in the coding region of human TIM1 include an insertion, 157insMTTTVP (allele 1), a deletion 195ΔThr, 157insMTTVP, T140A, V161A, V167I, T172A, and N258D (see paragraph 37, page 8-9) and assert that most of these variations are located within exon 3. The specification asserts that Tim gene sequence is other than human Tim-1, allele 1. The specification asserts that in combination with HAV seropositivity, allele 1 is protective for atopy and the presence is indicative that an individual may benefit from exposure to HAV for atopy treatment and/or prophylaxis and determination of

the presence of the allele may be determined by various methods known in the art (see page 10, paragraph 42). Although determination of allele is routine in the art, predictably correlating an allele to atopy in any human individual is unpredictable and the specification does not predictably correlate each of these polymorphisms with atopy in any human individual.

The specification teaches there are a number of methods that are available for analyzing nucleic acid for the presence of a specific sequence. The specification teaches that amplification with detectable labels, oligonucleotide ligation, hybridization to any array are available (see paragraph 53-54, 56, pages 13-14). However, the specification does not predictably correlate a method for screening for predisposition to atopy in any human by detecting "any" polymorphism within the TIM-1.

The specification demonstrates a working example of association between atopy and 157insMTTTVP in a cross-sectional study of 375 individuals who were tested for serologic evidence of atopy and prior HAV infection. The specification demonstrates that HAV infection protects against atopy but only in individuals with the 157insMTTTVP Tim-1 allele (see paragraph 194, pages 54-55). Although, table 1 of the specification demonstrates that HAV positive subjects with the 157insMTTTVP Tim-1 allele are associated with protection against atopy, table S3 and S4 demonstrate that 157insMTTTVP is predictably correlative for only the Caucasian population that is HAV positive and that are homozygous for the 157insMTTTVP allele. Table S4 demonstrates that neither the HAV negative or HAV positive population of Asians subjects is statistically relevant to diagnosis a predisposition to any immunological disorder or atopy and Table S3 demonstrates that the only statistically relevant data in the Caucasian subjects is for Caucasians subjects with HAV that are homozygous for

157insMTTTVP allele. The specification asserts that the African American sample size was too small to present separately (see paragraph 199, page 56).

The specification does not teach the association of any polymorphism, other than the 157insMTTTVP allele, in TIM-1 gene with the risk of developing atopy. The specification does not teach an association of any polymorphism with an increased likihood of developing atopy.

The following is unclear from the teaching in the specification. The specification does not teach which polymorphisms other than 157insMTTVIP allele of the TIM-1 gene is predictably correlative to diagnosing a predisposition to atopy in all ethnicities. The specification teaches only a statistically relevant association of 157insMTTTVP in Caucasian subjects that are homozygous for the allele that are HAV positive and have protection against atopy. The specification does not teach an association with any other polymorphism with TIM-1 and any atopy or association with presence or absence of HAV. It is unclear which polymorphism would be predictive of screening for predisposition to atopy in "any" individual.

The specification envisions hypothetical situations where any polymorphism within the TIM-1 gene could determine the presence of atopy. The specification appears to be conceiving of possible scenarios where the presence of any polymorphism in TIM-1 would indicate the presence – or absence – of atopy, however, it is unclear how one of skill in the art would determine which polymorphism of TIM-1 gene would screen for predisposition to atopy.

The unpredictability of the art, the state of the prior art, and the level of skill in the art

While the state of the art and level of skill in the art with regard to detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any

particular polymorphism with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art does not teach any association between any polymorphism in TIM-1 gene and predisposition in any individual for atopy.

While the claims of the instant application are broad and encompass analysis of any human, the instant specification provides evidence only of a statistically significant association between the 157ins MTTTVP allele of TIM-1 of SEQ ID No. 22, and protection against atopy in Caucasians that are positive for HAV.

Because the claims are drawn to methods that encompass the analysis of any polymorphism of TIM-1 gene, it is relevant to note that there are multiple polymorphic positions identified in TIM-1. A Gene Card search of TIM-1 gene indicates that there are 135 SNPs of TIM-1 gene (see page 7 of Gene Card). The instant specification does not teach any association of these 135 polymorphisms with atopy.

Additionally, the prior art teaches that there are many parameters that need to be evaluated prior to using a genetic test to determine a disease and that these parameters yield gaps in information that are needed to complete a thorough screening of a genetic test. Post filing art, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular

disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1st column, 1st and 2nd full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (see page 479, 2nd column, last paragraph). Additional post filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, 2004, Vol 18, page 20) teach that it strikingly common for follow-up studies to find gene-disease associations wrong (see page 2, 1st paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (see page 2, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical method, should be included in the gene association studies (see page 3, 2nd paragraph).

Furthermore, Ionnidis (Plost Med, 2005, 2(8):e124) teach that most published research findings are false. Ionnidis et al. teach that ill-founded strategy of claiming conclusive research finding solely on the basis of a single study assed by formal statistical significance represented and summarized by p values (see pg. 0696, 2nd column, 1st full para.) Ionnidis et al. teach that research findings are likely to be true that in fields that undertake large studies, such as randomized controlled trials (several thousand subjects randomized) than in small studies such as sample sizes 100 fold or smaller (see pg. 0697, 3rd column, 2nd full para.) Ionnidis et al. teaches

that what matters is the totality of evidence and that statistical significance of a single study only gives a partial picture (see pg. 0701, 1st column). Additionally, Hattersley et al. (Lancet, 2005, vol 366, pp. 1315-1323) teaches that the key quality in an association study is sample size (see page 1318, 2nd column, 1st full paragraph). Hattersley et al. teach that sample sizes of thousands are needed to detect variants that are common but have low relative risk and teach that allelic odds ratio of 1.1 to 2.0 requires the number of controls to be in thousands (see page 1318, 2nd column, 1st full paragraph and table 3). Hattersley et al. teach that apparent studies in identifying interesting associations with studies much smaller than implied by table 3 (in the thousands) might suggest that calculations are too pessimistic and small initial studies rarely find the correct result and even when they do they are likely to overestimate the true effect size (see page 1318, 1st column, 1st full paragraph). Hattersley et al. further teaches that emphasis has been on the need for greater stringency in the association studies in order to prove a given association and suggest a p value of $5x10^{-8}$, however arguments from Bayesian perspective suggest that $5x10^{-5}$ should be sufficient to constrain the false discovery rate. It is further relevant to point out that Hegele (2002) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

Based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate any polymorphism within the TIM-1 gene with atopy, as the specification does not teach a large sample size or confidence levels greater than 95% for every polymorphism of the TIM-1 gene or the association of TIM-1 with atopy. The specification only teaches a large sample size with statistically significant data for the analysis of an association between HAV positive subjects with the 157insMTTTVP allele in a Caucasian population.

Furthermore, the post filing art teaches the unpredictability of determining an association in different ethnical groups with any polymorphism in TIM-1 gene with atopy. Noguchi et al. (Genes and Immunity (2003) 4:170-173) teach that the seven different polymorphism within the TIM-1 gene, including two insertions and deletions were found not associated with the development of asthma in Japanese asthmatic families that showed strong evidence for linkage of atopic asthma (see page 172, right column, last paragraph). Noguchi et al. teach that no observation between hHAVcr-1(TIM-1) polymorphisms and atopic asthma in Japanese asthmatic families was associated and these polymorphisms may be related to susceptibility to hepatitis A infection and teach that further studies of different populations are needed to elucidate the role of polymorphisms in the development of atopic and infectious diseases (see page 172, 2nd column, last paragraph).

Applicant's own post-filing art, Umetsu et al. (Ann NY Acad Sci, 2004, 1029:88-93), teach that in the total population there was no association of the TIM-1 insertion (157insMTTTVP) with atopy. Umetsu et al. teach that if an individual had one or two copies of the insertion polymorphism in TIM-1, he or she was as likely to be atopic as those who had no copies of the insertion polymorphism, however when assayed for HAV seropositive and

seronegative, it was found that a significant inverse association of the insertion and atopy. Umetsu et al. teach that the HAV seropositive subjects who had one or two copies of the insertion were much less likely to be atopic that those who had no copies and the HAV negative population was no associated with any protection against atopy. (see page 92, 1st full paragraph). Thus, Umetsu et al. teach that the only individuals that are HAV positive are predictably correlative to protection against atopy in individuals that have the polymorphic insertion in TIM-1 gene.

Graves et al. (J Allerg Clin Immunol 2005, vol 118, pages 650-656) teach a study to evaluate multiple polymorphism in TIM1 gene and the association with atopy. Graves et al. teach association with atopy and one polymorphism, 15bp insertion/deletion of TIM-1 (see page 655, 1st column, 1st full paragraph). Graves et al. teach that in a Korean case control study increased risk for atopic dermatitis was found but not for asthma with the 15bp deletion of the TIM-1 gene (see page 655, 1st column, 1st full paragraph). Graves et al. teach analysis of seven different polymorphisms of TIM-1 gene and demonstrate that several polymorphisms are not statistically relevant, for example TIM1_1, 2, 5, and 7 (see table E2). Graves et al. teach that their findings need to replicated in other studies and the major limitation of the analysis is related to ethnic heterogeneity reflected in the Tucson population. Therefore, Graves et al. teach that multiple polymorphisms of TIM-1 gene that are not associated with atopy or immunological disorder and teach that further studies of an association of TIM-1 with atopy need to be completed.

The claims are broadly drawn to screening for predisposition to any individual of atopy. The example presented in the specification provides an analysis of the 157insMTTTVP allele of

TIM-1 gene with regard to HAV positive Caucasians subjects and atopy. The prior art teaches that confidence levels greater than 95% are necessary for predictably associating genetic tests with diseases. The instant specification shows the unpredictability in associating any polymorphism, including 157insMTTTVP allele of TIM-1 gene with any individual for any type of atopic immunological disorder. For example, table S3 demonstrates that 157insMTTTVP is not associated with atopy protection any individual that is not HAV positive and demonstrates that the 157insMTTTVP is not associated with atopy protection in every ethnic group (see table S4 and lack of African American analysis). Thus, based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate any polymorphism within the TIM-1 gene with any type of immunological disorder, as the specification does not teach a large sample size or confidence levels greater than 95% for every polymorphism of the TIM-1 gene or the association of TIM-1 with any type of immunological disorder. The specification teaches a large sample size with statistically significant data for the analysis of an association between HAV positive subjects with the 157insMTTTVP allele in the TIM-1 in a Caucasian population for protection against atopy.

Quantity of Experimentation

Given the lack of guidance in the specification with regard to association of any polymorphism in the TIM-1 gene with any atopic immunological disorder in any individual along with the evidence in the art that demonstrates that not every polymorphism of TIM-1 gene is associated with an immunological disorder, the quantity of experimentation in this area is extremely large. The skilled artisan would have to perform an extremely large study and include different populations and familial studies for each of the polymorphisms of the TIM-1 gene (135

polymorphisms known) to determine if in fact there was either an association between the polymorphism in individuals and atopy. The results of such a study are clearly unpredictable as evidence by the applicant's own post filing art (which reflects the current state of the art) and the teachings in the specification with regard to correlating the 157insMTTTVP allele of TIM-1 with different ethnic groups and HAV negative individuals to atopy much less any immunological disorder. Graves et al. teach that multiple polymorphisms of TIM-1 gene that are not associated with atopy or immunological disorder and teach that further studies of an association of TIM-1 with atopy need to be completed. Furthermore, Noguchi et al. teach that no observation between hHAVcr-1(TIM-1) polymorphisms and atopic asthma in Japanese asthmatic families was associated and these polymorphisms may be related to susceptibility to hepatitis A infection and teach that further studies of different populations are needed to elucidate the role of polymorphisms in the development of atopic and infectious diseases (see page 172, 2nd column, last paragraph). In the instant case, it would be unpredictable as to whether or not 157insMTTTVP would be responsible for determining the predisposition to atopy in any individual without also determining if the individual was HAV positive or negative.

In order to practice the invention as broadly as it is claimed, the skilled artisan would have to determine the sequence of the human TIM-1 in each individual and then determine which polymorphism would detect any type of immunological disorder. The skilled artisan would then have to screen variants to determine those that are associated with a susceptibility to any atopic immunological disorder in all populations. The skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such expression levels would predictable determine a susceptibility to all or any atopy. Given the lack

of guidance in the specification and the post filing art with respect to accurately testing genetic diseases, such analysis is replete with unpredictable experimentation and is considered undue.

Response to Arguments

5. The response traverses the rejection on pages 5-6 of the remarks mailed 08/05/2008. The response asserts on page 6 that the conclusions of applicant's data were published in a peer reviewed journal, Nature and submit that they have proven the validity of their statistical analysis by publishing the same data being challenged by the office. This response has been thoroughly reviewed but not found persuasive. It is noted that the paper published in Nature has not been provided in the application, however the examiner has provided it in response to these remarks. The examiner has agreed that the specification has provided statistical analysis for determining a Caucasian or Asian's predisposition to atopy protection by detecting the presence of homozygous polymorphism of 157insMTTTVP (polymorphism 1, SEQ ID No. 22), of TIM-1 in a hepatitis virus A positive Caucasian individual, wherein the presence of the 157insMTTTVP insertion is indicative of a Caucasian's predisposition to protect against atopy however neither the post filing art or published art in Nature predictably correlate nor provide statistical analysis that provide an association of a representative number of polymorphisms in the TIM-1 gene with atopy in a human. Additionally, McIntire et al. (Nature, 2003, vol. 425, p. 576) teach that only in individuals that have the 157insMTTTVP variant and are HAV seropositive protective against atopy is their an association (see 2nd column, 1st full paragraph). McIntire et al. further teaches that the only stastitically significant data is the subgroup analysis of Caucasians and Asians who are seropositive for HAV (see table 1). Thus, the published report by applicant in Nature confirm the examiner's validity of the statistical analysis published in the patent application. It is

noted, the claims are broadly drawn to a screening for human's predisposition to atopy by analyzing a presence of a TIM-1 polymorphism, which requires the knowledge that a polymorphism of TIM-1 is predictive of atopy and neither the article published in nature nor the specification provide a representative number of polymorphisms within the TIM-1 gene that are predictably associated with atopy in all populations, regardless of HAV presence or absence.

The response asserts that the other points raised by the office were presented in the last response. It is noted that each of these remarks were addressed in the office action mailed 03/05/2008.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 112-Written Description

6. Claims 1, 4, 7 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was previously presented in section 8 of the office action mailed 10/04/2007 and is reiterated below.

> Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

The rejected claims are broadly drawn to methods for diagnosing predisposition to any atopic immunological disorder comprising determining any polymorphism in any individual

(claim 1). The claims are broadly drawn to methods comprising the detection of a variety of nucleic acids, including any polymorphic variant of TIM-1 gene that is associated with any type of atopy. The claims are limited to probes that specifically bind to exon 3 of TIM-1 gene (claim 23) or probes that bind to MTTTVP sequence (claim 4), however the limitation of probes that specifically bind to a nucleic acid sequence or exon 3 does not limit the claims to detection of a specific polymorphism of TIM-1 gene as the claims merely require analyzing a biological sample with a probe that specifically binds to a nucleic acid sequence and this does not limit the polymorphism that is indicative of atopic immunological disorder. The claims merely require analyzing a probe that binds to a nucleic acid but the claims do not require the presence of the specific probe binding to the nucleic acid is indicative of predisposition to develop an atopic immunological disorder.

When the claims are analyzed in light of the specification, the instant invention encompasses methods comprising the analysis and detection of an enormous and wide variety of nucleic acid sequences. The claims are broadly drawn to a method that encompass a plurality of nucleic acids an extremely large genus of polymorphic variants of the TIM-1 gene with any nucleotide content (A or G or C or T) at any position within the TIM-1 gene. Thus the claims encompass the detection of any of different nucleic acids wherein the nucleic acid sequence is correlated with an association of disease. Nucleic acids of such a large genus have not been taught by the specification.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The instant specification provides the sequence of SEQ ID No. 18, 20, 22,

24, 26, and 28. The specification also provides the amino acid sequence of TIM-1 as SEQ ID No. 19, 21, 23, 25, 27, and 29. The specification provides analysis of the insertion of the following amino acid sequence of MTTTVP at position 157 and indicating that this insertion is indicative of association of disease. The specification does not teach any association with any other polymorphic variation disclosed in the specification, for example deletion 195ΔThr, 157insMTTVP, T140A, V161A, V167I, T172A, and N258D that are indicative of association of atopic immunological disorders.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence, gene name, and specific polymorphic position), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification provides only the polymorphic sequences of the human TIM1 gene (SEQ ID NO: 18, 20, 22, 24, and 26) and the encoded amino acid sequence (SEQ ID NO: 19, 21, 23, 25, 27). The specification does not provide any characteristics that would allow one to identify any other genes from another organism or any particular portions or fragments or variants of the disclosed sequence that would allow for the diagnosis of any type of atopic immunological disorder based on detection of the non-disclosed gene. Furthermore, the art discloses that there are 135 SNPs known for the TIM-1 gene (see GeneCard, page 7). Neither the specification nor the prior art teach an association with any of these SNPs with any type of immunological disorder or atopy.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117

> F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, because of the lack of any analysis regarding polymorphisms of the TIM-1 gene other than the insertion of the amino acid sequence of MTTTVP at position 157 of the amino acid sequence, one of skill in the art cannot envision the detailed chemical structure of the nucleic acid encompassed by the claimed methods, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that such nucleic acids are part of the invention and reference to a potential method for identification. The particular nucleic acids are themselves required.

In conclusion, the limited information provided regarding the nucleic acids of the claimed methods is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method of diagnosis for the predisposition of immunological disorder in an individual by determining the presence of a polymorphism in TIM-1 other than methods using detection of the insertion of the amino acid sequence MTTTVP at position 157 of TIM-1.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Response to Arguments

7. The response traverses the rejection on pages 7 of the remarks mailed 08/05/2008. The response asserts that while there may be sequences within the genus defined by TIM-1 polymorphism that will not be significantly associated with atopy, the courts have clearly taught

that even in unpredictable arts the specification does not have to disclose every species of a genus. This response has been thoroughly reviewed but not found persuasive. It is noted that the examiner is not suggested or requiring applicant to provide every species of the large genus encompassed by the claims, however a representative number of the claimed genus must be described. In the instant case, the claims require polymorphisms within or specific to TIM-1 gene that are associated with atopy, however a representative number of nucleic acids, of this large genus of polymorphic variants of TIM-1 gene and their association with atopy, is not described in the specification. The specification merely discloses one polymorphism,157insMTTTVP, associated with protection against but not diagnostic of atopic immunological conditions, which is not a representative number of the large genus of TIM-1 polymorphisms. Furthermore the one polymorphism, 157ins MTTTVP disclosed by the specification is not associated with atopic immunological conditions in all populations. Therefore the specification has not described a representative number of polymorphic species of TIM-1 gene that are associated with atopy

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

8. No claims are allowable.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAE BAUSCH whose telephone number is (571)272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application

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/Sarae Bausch/
Primary Examiner, Art Unit 1634